

## **APPENDIX A**

AU BUREAU CANADIEN  
DES BREVETS

Brevet canadien No. : 2,406,592

Émis le : 30 septembre 2003

Demandeur : DUCHESNAY INC.

Titre : METHOD OF PREPARING PHARMACEUTICAL  
DOSAGE FORMS CONTAINING MULTIPLE  
ACTIVE INGREDIENTS

Notre dossier : 11621.86

**AU COMMISSAIRE DES BREVETS  
OTTAWA, CANADA**

Le 28 septembre 2006

**PAIEMENT DE LA TAXE PÉRIODIQUE**

Monsieur,

Veuillez trouver ci-joint le versement de \$ 100.00 (grande entité) en règlement de la taxe de maintien due le 4 octobre 2006 pour la 4e année du brevet mentionné en rubrique.

Veuillez débiter le montant ci-haut à notre compte N° 600000102.

Si le paiement soumis avec la présente lettre ne suffit pas à couvrir toutes les taxes pour lesquelles un paiement est requis de façon explicite ou implicite, le commissaire est autorisé à prélever la somme manquante sur le compte no. 600000102 déjà au dossier.

Veuillez agréer, Monsieur le Commissaire, nos salutations les plus distinguées.

Par / By: \_\_\_\_\_

GOUDREAU GAGE DUBUC  
Agents de Brevets / Patent Agents

JHD/jg  
Tél. : (514) 397-4306

IN THE CANADIAN  
PATENT OFFICE

Canadian patent No : 2,406,592

Issued on : September 30, 2003

Applicant: DUCHESNAY INC.

Title : METHOD OF PREPARING PHARMACEUTICAL  
DOSAGE FORMS CONTAINING MULTIPLE  
ACTIVE INGREDIENTS

Our File : 11621.86

2028886

**THE COMMISSIONER OF PATENTS  
OTTAWA, CANADA**

September 28, 2006

**PAYMENT OF MAINTENANCE FEE**

Sir:

Please find enclosed the payment of 100.00\$ (Large Entity) for the maintenance fee due on October 4, 2006 for the 4th year of the above-noted patent.

Please debit the amount above to our Deposit Account N° 600000102.

Should the fees submitted with this letter be insufficient to cover all of the fees for which payment is explicitly or implicitly requested by this letter, the Commissioner is authorized to charge the amount of the insufficiency to our Deposit account no. 600000102 already on file.

Respectfully submitted,

*Goudreau Gage Dubuc*

Industry  
Canada

AMJ..... YMD

2006/09/28

275 - 06



CIPO

OPIC

A000656627

**AU BUREAU CANADIEN  
DES BREVETS**

**IN THE CANADIAN  
PATENT OFFICE**

1476675  
SA

Brevet canadien No. : 2,406,592

Canadian patent No : 2,406,592

Émis le : 30 septembre 2003

Issued on : September 30, 2003

Demandeur : DUCHESNAY INC.

Applicant: DUCHESNAY INC.

Titre : METHOD OF PREPARING PHARMACEUTICAL  
DOSAGE FORMS CONTAINING MULTIPLE  
ACTIVE INGREDIENTS

Title : METHOD OF PREPARING PHARMACEUTICAL  
DOSAGE FORMS CONTAINING MULTIPLE  
ACTIVE INGREDIENTS

Notre dossier : 11621.86

Our File : 11621.86

AU COMMISSAIRE DES BREVETS  
OTTAWA, CANADA

THE COMMISSIONER OF PATENTS  
OTTAWA, CANADA

Le 30 septembre 2005

September 30, 2005

**PAIEMENT DE LA TAXE PÉRIODIQUE**

**PAYMENT OF MAINTENANCE FEE**

Monsieur,

Sir:

Veuillez trouver ci-joint le versement de \$ 100.00  
(grande entité) en règlement de la taxe de maintien due  
le 4 octobre 2005 pour la 3e année du brevet mentionné  
en rubrique.

Please find enclosed the payment of 100.00\$  
(Large Entity) for the maintenance fee due on October 4,  
2005 for the 3rd year of the above-noted patent.

Veuillez débiter le montant ci-haut à notre  
compte N° 600000102.

Please debit the amount above to our Deposit  
Account N°600000102.

Veuillez agréer, Monsieur le Commissaire, nos  
salutations les plus distinguées.

Respectfully submitted,

*Goudreau Gage Dubuc*

Par / By: \_\_\_\_\_

**GOUDREAU GAGE DUBUC**  
Agents de Brevets / Patent Agents

JHD/jg  
Tél. : (514) 397-4306

Industry  
Canada

AMU ... ... YMU



2005/09/30

277 - 05

CIPQ

OPIC

B000527118

AU BUREAU CANADIEN  
DES BREVETS

IN THE CANADIAN  
PATENT OFFICE

Brevet canadien No. : 2,406,592

Émis le : 30 septembre 2003

Canadian patent No : 2,406,592

1225993  
LWPT

Demandeur : DUCHESNAY INC.

Titre : METHOD OF PREPARING PHARMACEUTICAL DOSAGE FORMS CONTAINING MULTIPLE ACTIVE INGREDIENTS

Notre dossier : 11621.86

Applicant : DUCHESNAY INC.

Title : METHOD OF PREPARING PHARMACEUTICAL DOSAGE FORMS CONTAINING MULTIPLE ACTIVE INGREDIENTS

Our File : 11621.86

AU COMMISSAIRE DES BREVETS  
OTTAWA, CANADA

Le 1er octobre 2004

THE COMMISSIONER OF PATENTS  
OTTAWA, CANADA

October 1, 2004

**PAIEMENT DE LA TAXE PÉRIODIQUE**

Monsieur,

Veuillez trouver ci-joint le versement de \$ 100.00 (grande entité) en règlement de la taxe de maintien due le 4 octobre 2004 pour la 2e année du brevet mentionné en rubrique.

Veuillez débiter le montant ci-haut à notre compte N° 600000102.

Veuillez agréer, Monsieur le Commissaire, nos salutations les plus distinguées.

**PAYMENT OF MAINTENANCE FEE**

Sir:

Please find enclosed the payment of 100.00\$ (Large Entity) for the maintenance fee due on October 4, 2004 for the 2th year of the above-noted patent.

Please debit the amount above to our Deposit Account N° 600000102.

Respectfully submitted,

Par / By: \_\_\_\_\_

**GOUDREAU GAGE DUBUC**  
Agents de Brevets / Patent Agents

JHD/jg  
Tél. : (514) 397-4306



2004/10/01

279 - 04

A000279073

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Industry Canada  
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GOUDREAU GAGE DUBUC  
Tour de la Bourse  
Bureau 3400  
C.P. 242, 800 Place-Victoria  
MONTREAL Quebec  
H4Z 1E9

Date : 2004/06/07

Date de dépôt/Filing Date : 2002/10/04

Votre référence/  
Your Reference : 11621.86

Titre de l'invention/  
Title of Invention : METHOD OF PREPARING PHARMACEUTICAL DOSAGE FORMS CONTAINING MULTIPLE ACTIVE INGREDIENTS

Montant dû/Amount Due : \$100.00

Date limite de paiement/  
Payment Due Date : 2004/10/04

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N° de demande/Application No. : 2,406,592

**OBJET: TAXE DE MAINTIEN**

La présente a pour but de vous rappeler que pour maintenir votre demande en vigueur, vous devez payer la taxe annuelle au plus tard à la date d'anniversaire du dépôt, à compter du 2e anniversaire.

Vous pouvez payer annuellement ou à l'avance les taxes de maintien pour un nombre d'années donné.

L'omission de payer cette taxe dans les délais fixés résultera en l'abandon de la demande de brevet.

Veuillez prendre note que vous ne recevrez pas d'autre rappel concernant la demande de brevet susmentionnée.

Pour de plus amples renseignements, veuillez communiquer avec le Bureau canadien des brevets au (819) 953-8095.

**SUBJECT: MAINTENANCE FEE**

You are reminded that, in order to maintain the patent application in force, an annual fee must be paid on or before the anniversary of the filing date, starting with the second anniversary.

The maintenance fees can be paid yearly or for any number of years in advance.

Failure to pay within the prescribed time limit will lead to the abandonment of the patent application.

Please note that this is the only reminder notice that will be issued for this particular application.

Should you require more information, please do not hesitate to contact the Canadian Patent Office at (819) 953-8095.

Commissaire aux brevets/Commissioner of Patents

Canada

O P I C  C I P O



Direct Dial: (514) 397-7613  
Internet: [email@ggd.com](mailto:email@ggd.com)  
Your Ref.:  
Our Ref.: 11621.86



General Partnership  
Patent and Trademark Agents

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Quebec City  
140 Grande Allée Est  
Suite 300  
Québec, Canada G1R 5M8  
Telephone (418) 640-2000

Subject: Canadian Patent Application S.N. 2,406,592  
Classification: 07A61J-00003/06  
Allowed Date: June 23, 2003  
Applicant: DUCHESNAY INC.  
Title: METHOD OF PREPARING PHARMACEUTICAL DOSAGE  
FORMS CONTAINING MULTIPLE ACTIVE INGREDIENTS

Sir:

Please debit the amount of \$300.00 from our Deposit Account no. 600000102 in payment of the final fee of the above-noted application.

Respectfully submitted,

(Signature) Gage Dubuc  
Goudreau Gage Dubuc

AML/fi



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du Canada

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d'Industrie Canada

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Canadian

Intellectual Property

Office

An Agency of

Industry Canada

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GOUDREAU GAGE DUBUC  
Tour de la Bourse  
Bureau 3400  
C.P. 242, 800 Place-Victoria  
MONTREAL Quebec  
H4Z 1E9

Date : 2003/06/23

Classification :

## AVIS D'ACCEPTATION/NOTICE OF ALLOWANCE

N° de demande/Application No. : 2,406,592

Date de dépôt/Filing date : 2002/10/04

Votre référence/  
Your Reference : 11621.86

Titre de l'invention/  
Title of Invention : METHOD OF PREPARING PHARMACEUTICAL DOSAGE FORMS CONTAINING MULTIPLE ACTIVE INGREDIENTS

Propriétaire(s)/Owner(s) : DUCHESNAY INC.

Revendications/Claims : 010

Examiné tel que modifié/  
Examined as amended : 2003/05/09

La demande de brevet susmentionnée a été jugée acceptable.

Il faut payer la taxe finale de CENT CINQUANTE DOLLARS (150 \$) ou de TROIS CENT DOLLARS (300 \$) selon que le demandeur est une petite entité ou une grande entité, et ce dans les six mois suivant la date du présent avis. Autrement la demande sera réputée abandonnée en vertu de l'alinéa 73(1)(f) de la Loi sur les brevets.

Une taxe additionnelle de quatre dollars par page excédant 100 pages du mémoire descriptif et dessins devra aussi être payée.

Le brevet sera délivré au nom du dernier propriétaire inscrit à nos dossiers qui a fourni une documentation acceptable, au plus tard à la date du paiement de la taxe finale, conformément à l'article 41 des Règles sur les brevets.

La réponse au présent avis doit comprendre l'identification complète de la demande et la date de l'avis.

La publication des brevets canadiens délivrés dans la Gazette du Bureau des brevets peut comprendre aussi une note concernant la mise en vente d'un brevet ou de sa licence. Si vous désirez profiter de ce service gratuit, veuillez l'indiquer au moment de payer la taxe finale.

The above application for patent has been found allowable.

The final fee of ONE HUNDRED AND FIFTY DOLLARS (\$150.00) or THREE HUNDRED DOLLARS (\$300.00) depending upon whether the applicant is a small entity or a large entity must be paid within six months following the date of this notice. Otherwise the application will be deemed to be abandoned pursuant to paragraph 73(1)(f) of the Patent Act.

An additional fee of four dollars per page over 100 pages of specification and drawings must also be paid.

The patent shall issue to the last registered owner who has submitted acceptable documentation on or before the date that the final fee is paid (as pursuant to Section 41 of the Patent Rules).

A reply to this notice must include full identification of the application including the date of the notice.

The publication of issued Canadian patents in the Patent Office Record can also include an indication that the patent is available for licence or sale. If you wish to take advantage of this free service, please indicate this when paying the final fee.

Commissaire aux brevets/Commissioner of Patents

Canada

O P I C  C I P O

008

## IN THE CANADIAN PATENT OFFICE

Can. Pat Appl S. N.: 2,406,592

Industry  
CanadaIndustry  
Canada

2003/05/09

Filed: October 4, 2002



133 - 03

Applicant: DUCHESNAY INC.

CIPO

OPIC

A000023587

Title: METHOD OF PREPARING PHARMACEUTICAL DOSAGE FORMS CONTAINING MULTIPLE ACTIVE INGREDIENTS

Classification: 07A61J-00003/06

Our file: 11621.86 AML/hp

May 9, 2003

THE COMMISSIONER OF PATENTS  
OTTAWA CANADA

SIR:

SUPPLEMENTARY AMENDMENT

Following our letter dated April 15, 2003, please amend the above-noted application as follows:

**IN THE CLAIMS:**

Kindly substitute page 14 of the set of claims for the corresponding page 14 of the set of claims presently on file.

**REMARKS:**

Claims 1-10 are still in the case.

In claim 7, "The method of any one of claims 1 to 6..." has been changed to -- The method of claim 6 --.

In claim 8, "The method of any one of claims 1 to 6..." has been changed to -- The method of claim 7 --.

- 2 -

Consequently, it is respectfully submitted that all claims are now in condition for allowance and such action is respectfully urged.

Respectfully submitted,  
DUCHESNAY INC.

By: Alain M. Leclerc  
GOUDREAU GAGE DUBUC

Alain M. Leclerc, Patent Agent  
**GOUDREAU GAGE DUBUC**  
3400 Stock Exchange Tower  
P.O. Box 242, Victoria Square  
Montréal, Québec, Canada H4Z 1E9  
Telephone: (514) 397-7675  
E-mail: aleclerc@ggd.com

- (d) mixing said granules with at least one other active ingredient and at least one other excipient so as to obtain a granular mixture;
- (e) forming said granular mixture into unitary dosage forms.

6. The method of any one of claims 1 to 5 wherein the step of forming said granular mixture into unitary dosage forms comprises compressing said granular mixture into a tablet shape.
7. The method of claim 6 wherein the tablet shape is provided with a coating.
8. The method of claim 7 wherein said coating is an enteric coating.
9. The method of any one of claims 1 to 5 wherein the step of forming said granular mixture into unitary dosage forms comprises loading said granular mixture into an open capsule and thereafter closing said capsule.
10. The method of any one of claims 1 to 9 wherein the active ingredients comprise equal parts of Pyridoxine HCl and Doxylamine Succinate.

## IN THE CANADIAN PATENT OFFICE

PPB

**Can. Pat Appn S. N.:** 2,406,592

2003/04/15

112- 03

D000007512

**Filed:** October 4, 2002

OPIC

**Applicant:** DUCHESNAY INC.**Title:** METHOD OF PREPARING PHARMACEUTICAL DOSAGE FORMS CONTAINING MULTIPLE ACTIVE INGREDIENTS**Classification:** 07A61J-00003/06**Our file:** 11621.86 AML/hp

April 15, 2003

**THE COMMISSIONER OF PATENTS**  
**OTTAWA**                           **CANADA**

**SIR:**

In response to the Office Action dated March 3, 2003, please amend the above-noted application as follows:

**IN THE CLAIMS:**

Kindly substitute the enclosed set of claims for the corresponding set of claims presently on file.

**REMARKS:**

Claims 1-10 are now in the case.

The Examiner is rejected claims 1 to 9 and indicated that claims 10 to 12 are allowable. In order to place this case in condition for allowance, applicant has introduced the subject matter of claim 10 to each of independent claims 1 to 5. Thus, claims 6 to 9 are dependent on allowable claims. Claim 10 is cancelled. Claim 11 is renumbered as claim 10. Claim 12 is cancelled.

- 2 -

Consequently, it is respectfully submitted that all claims are now in condition for allowance and such action is respectfully urged.

Finally, in response to section 29 requirements, applicant advises that at this time there exists no corresponding US, EPO or any other regional office applications.

Respectfully submitted,  
DUCHESNAY INC.

By: Goudreau Gage Dubuc  
GOUDREAU GAGE DUBUC

Alain M. Leclerc, Patent Agent  
**GOUDREAU GAGE DUBUC**  
3400 Stock Exchange Tower  
P.O. Box 242, Victoria Square  
Montréal, Québec, Canada H4Z 1E9  
Telephone: (514) 397-7675  
E-mail: aleclerc@ggd.com

**WHAT IS CLAIMED IS:**

1. A method for the preparation of pharmaceutical dosage forms comprising Pyridoxine HCl and Doxylamine Succinate as active ingredients, said method comprising the steps of:
  - (a) mixing said active ingredients and at least one chosen excipient so as to obtain a powdered mixture;
  - (b) compacting said powdered mixture in a roller compactor apparatus to obtain a compacted product;
  - (c) breaking and sieving said compacted product to a chosen mesh size to obtain similar sized granules;
  - (d) forming said granules into unitary dosage forms.
2. A method for the preparation of pharmaceutical dosage forms comprising Pyridoxine HCl and Doxylamine Succinate as active ingredients, said method comprising the steps of:
  - (a) mixing said active ingredients and at least one chosen excipient so as to obtain a powdered mixture;
  - (b) compacting said powdered mixture in a roller compactor apparatus to obtain a compacted product;
  - (c) breaking and sieving said compacted product to a chosen mesh size to obtain similar sized granules;
  - (d) mixing said granules with at least one chosen excipient so as to obtain a granular mixture;
  - (e) forming said granular mixture into unitary dosage forms.
3. A method for the preparation of pharmaceutical dosage forms comprising Pyridoxine HCl and Doxylamine Succinate as active ingredients, said method comprising the steps of:
  - (a) mixing said active ingredients so as to obtain a powdered mixture;

- (b) compacting said powdered mixture in a roller compactor apparatus to obtain a compacted product;
- (c) breaking and sieving said compacted product to a chosen mesh size to obtain similar sized granules;
- (d) mixing said granules with at least one chosen excipient so as to obtain a granular mixture;
- (e) forming said granular mixture into unitary dosage forms.

4. A method for the preparation of pharmaceutical dosage forms comprising Pyridoxine HCl and Doxylamine Succinate as active ingredients, said method comprising the steps of:

- (a) mixing at least one of said active ingredients and at least one excipient so as to obtain a powdered mixture;
- (b) compacting said powdered mixture in a roller compactor apparatus to obtain a compacted product;
- (c) breaking and sieving said compacted product to a chosen mesh size to obtain similar sized granules;
- (d) mixing said granules with at least one other active ingredient so as to obtain a granular mixture;
- (e) forming said granular mixture into unitary dosage forms.

5. A method for the preparation of pharmaceutical dosage forms comprising Pyridoxine HCl and Doxylamine Succinate as active ingredients, said method comprising the steps of:

- (a) mixing at least one of said active ingredients and at least one excipient so as to obtain a powdered mixture;
- (b) compacting said powdered mixture in a roller compactor apparatus to obtain a compacted product;
- (c) breaking and sieving said compacted product to a chosen mesh size to obtain similar sized granules;

- (d) mixing said granules with at least one other active ingredient and at least one other excipient so as to obtain a granular mixture;
- (e) forming said granular mixture into unitary dosage forms.

6. The method of any one of claims 1 to 5 wherein the step of forming said granular mixture into unitary dosage forms comprises compressing said granular mixture into a tablet shape.
7. The method of any one of claims 1 to 6 wherein the tablet shape is provided with a coating.
8. The method of any one of claims 1 to 6 wherein said coating is an enteric coating.
9. The method of any one of claims 1 to 5 wherein the step of forming said granular mixture into unitary dosage forms comprises loading said granular mixture into an open capsule and thereafter closing said capsule.
10. The method of any one of claims 1 to 9 wherein the active ingredients comprise equal parts of Pyridoxine HCl and Doxylamine Succinate.

March 3, 2003

**GOUDREAU GAGE DUBUC**  
Tour de la Bourse  
Bureau 3400  
C.P. 242, 800 Place-Victoria  
MONTREAL Quebec  
H4Z 1E9

**Application No.** : **2,406,592**  
**Owner** : DUCHESNAY INC.  
**Title** : **METHOD OF PREPARING PHARMACEUTICAL DOSAGE FORMS CONTAINING MULTIPLE ACTIVE INGREDIENTS**  
**Classification** : A61J-3/06  
**Your File No.** : **11621.86**  
**Examiner** : Ishtiaque I. Rashid

IN ACCORDANCE WITH SUBSECTION 30(2) OF THE PATENT RULES, YOU ARE HEREBY NOTIFIED OF A REQUISITION BY THE EXAMINER. IN ORDER TO AVOID ABANDONMENT UNDER PARAGRAPH 73(1)(A) OF THE PATENT ACT, A WRITTEN REPLY MUST BE RECEIVED WITHIN 6 MONTHS AFTER THE ABOVE DATE.

This application has been examined taking into account applicant's correspondence dated December 9, 2002.

The number of claims in this application is 12.

A search of the prior art has revealed the following:

References Applied:

Canadian Patent Application

2224269                    Jan. 9, 1997                    A61K-31/565                    De Haan et al

De Haan et al disclose a method for the preparation of pharmaceutical dosage forms comprising multiple powdered active ingredients, said method comprising the steps of: mixing said active ingredients and at least one chosen excipient so as to obtain a powdered mixture; compacting said powdered mixture in a roller compactor apparatus to obtain a compacted product; breaking and sieving said compacted product to a chosen mesh size to obtain similar sized granules and forming said granules into unitary dosage forms. A step of mixing said granules with an excipient so as to obtain a granular mixture, before forming said granular mixture into unitary dosage forms is also disclosed in another embodiment of the invention.

The examiner has identified the following defects in the application:

Claims 1 to 6 do not comply with Paragraph 28.2(1)(b) of the Patent Act. De Haan et al disclosed the claimed subject matter before the claim dates.

From the above, it is clear that no novelty can be found in the claims.

Claims 7 to 9 do not comply with Section 28.3 of the Patent Act. The subject matter of these claims would have been obvious on the claim date to a person skilled in the art or science to which they pertain having regard to De Haan et al in light of common general knowledge. The major elements are found in De Haan whereas the fact that the resulting tablets are provided with an enteric coating is well known in the art and thus lacks an inventive step. The same can be said about the granular mixture which is placed into the capsules. These elements by themselves are so common in the pharmaceutical manufacturing industry, that they are not considered to be patentable.

Under Section 29 of the Patent Rules, applicant is requisitioned to provide an identification of any prior art cited in respect of the corresponding United States, European Patent Office and any other regional office applications and the patent numbers, if granted. Amendment to avoid references cited abroad may expedite the prosecution. If the particulars are not available to the applicant, the reason why must be stated. Accordingly, if the applicant did not apply for a patent in a foreign country, it must be stated.

The above requisitioned information must be provided regardless of the current status of the foreign applications.

Claims 10 to 12 appear to be acceptable at this point of the examination.

In view of the foregoing defects, the applicant is requisitioned to amend the application in order to comply with the Patent Act and the Patent Rules or to provide arguments as to why the application does comply.

Ishtiaque I. Rashid  
Patent Examiner  
(819) 953-0787  
2406592A.iir



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Date : 2003/02/17

GOUDREAU GAGE DUBUC  
Tour de la Bourse  
Bureau 3400  
C.P. 242, 800 Place-Victoria  
MONTREAL Quebec  
H4Z 1E9

## ACCUSE DE RECEPTION DE LA REQUETE D'EXAMEN ACKNOWLEDGEMENT OF REQUEST FOR EXAMINATION

N° de demande/Application No. : 2,406,592

Classification :

Votre référence/Your Reference : 11621.86

Titre de l'invention/  
Title of Invention : METHOD OF PREPARING PHARMACEUTICAL DOSAGE FORMS CONTAINING MULTIPLE ACTIVE INGREDIENTS

Propriétaire(s)/Owner(s) : DUCHESNAY INC.

Nous accusons réception de la requête et de la taxe prescrite.

L'examen de la demande suivra son cours.

Il serait à l'avantage du demandeur de fournir les détails de toutes les antériorités citées à l'égard de la demande correspondante aux États-Unis et en Europe lorsqu'elles seront disponibles. De plus, afin de faciliter la procédure d'examen de cette demande, il serait utile de nous envoyer une copie de toutes les citations qui ne sont pas des brevets.

Veuillez ne pas tenir compte du paragraphe précédent si vous avez déjà soumis les antériorités.

The Request for Examination and prescribed fee have been received.

Examination of the application will take place in due course.

It would be to an applicant's advantage to furnish particulars of the prior art cited in respect of the corresponding applications before the United States Patent Office and European Patent Office when such information becomes available. Furthermore, in order to assist in the examination of this application, a copy of all non-patent citations would be appreciated.

If prior art has already been submitted, please disregard the above paragraph.

L. Roussel

Canada

O P I C  C I P O

February 17, 2003

**GOUDREAU GAGE DUBUC**  
Tour de la Bourse  
Bureau 3400  
C.P. 242, 800 Place-Victoria  
MONTREAL Quebec  
H4Z 1E9

**Application No.** : **2,406,592**  
**Owner** : DUCHESNAY INC.  
**Title** : **METHOD OF PREPARING PHARMACEUTICAL DOSAGE  
FORMS CONTAINING MULTIPLE ACTIVE INGREDIENTS**  
**Classification** : A61J-3/06  
**Your File No.** : **11621.86**

Dear Sir/Madam:

Replying to your letter of December 9, 2002, a Special Order will be granted when the application is laid open and the application will be advanced out of its routine order for examination at that time.

Also, your request for examination and your request for an early laid-open date have been made of record. The laid-open date is April 17, 2003.

Yours truly,

Line Roussel  
Head, Exam Support, Unit 3  
(819) 997-7663



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C.P. 242, 800 Place-Victoria  
MONTREAL Quebec  
H4Z 1E9

Date : 2003/01/22

Votre référence/Your Reference :  
**11621.86**

**ENREGISTREMENT/REGISTRATION 05201964**

CESSION DROIT EXCLUSIF  
ASSIGNMENT FULL INTEREST

**DE/FROM** VEILLEUX, GISELE; SHULMAN, VICTOR; GERVAIS, ERIC

**A/TO** DUCHESNAY INC.

Un document a été enregistré au Bureau des brevets, visant le ou les numéros de brevet(s) et/ou de demande(s) de brevet, apparaissant ci-dessous.

**DEMANDE(S)/APPLICATION(S)**

2,406,592

A document has been registered in the Patent Office, against the following patent(s) and/or application(s) for patent.

SLAUDER

Commis aux cessions de brevets/Patent Assignment Clerk

Canada

OPIC CIPO

1020232

IN THE CANADIAN PATENT OFFICE

**Can. Pat. Appn. S.N.:** 2,406,592  
**Filed:** October 4, 2002 C/A # 6102  
**Applicant:** DUCHESNAY INC. K122  
**Title:** METHOD OF PREPARING PHARMACEUTICAL DOSAGE  
 FORMS CONTAINING MULTIPLE ACTIVE INGREDIENTS  
**Our File:** 11621.86

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DEPOT POUR REC. GEN.  
DU CANADA 033-13655  
0881-10 09-87913

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3702 B# 020 0001-002 3:02PM 12/12/02

6 Industrie Canada Industry Canada 6  
 OPIC CIPO

December 9, 2002

DEC - 9 2002 3 4 5

**THE COMMISSIONER OF PATENTS**  
**OTTAWA CANADA**

Sir:

Pursuant to Section 35 of the Patent Act, applicant hereby request the examination of the above-noted application. A voluntary amendment is also enclosed.

Pursuant to Section 28 (1) of the Patent Rules, applicant also requests the advancement of the examination in view of possible infringement. It is believed that failure to advance this application is likely to prejudice applicant's right.

Finally, according to section 10(2) of the Patent Act, the applicant hereby requests that the above-noted application be published as soon as possible.

Please debit the amount of \$500.00 from our Deposit Account no. 600000102 in payment of the prescribed fee of \$400.00 for filing the examination request and the prescribed fee of \$100.00 for the advancement requests.

Respectfully submitted

DUCHESNAY INC.

By:   
 GOUDREAU/GAGE DUBUC

Alain M. Leclerc  
 Patent Agent  
 (514) 397-7675

DEPOT POUR REC. GEN.  
DU CANADA 033-13655  
0881-10 09-87913

C/A # 6102  
 K122  
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## IN THE CANADIAN PATENT OFFICE

**6** Industrie  
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Canada  
CIPO **6**

**Can. Pat Appln S. N.:** 2,406,592

**DEC - 9 2002 3 4 5**

**Filed:** October 4, 2002

Deedster File
Name is Charged to

**Applicant:** Duchesnay Inc.

**Title:** METHOD OF PREPARING PHARMACEUTICAL DOSAGE  
FORMS CONTAINING MULTIPLE ACTIVE INGREDIENTS

**Classification:** Unknown

**Our file:** AML/11621.86

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December 9, 2002

**THE COMMISSIONER OF PATENTS  
OTTAWA                    CANADA**

**SIR:**

**VOLUNTARY AMENDMENT**

Applicant submit the following amendment to the above-noted patent application in order to correct typographical errors.

**IN THE DISCLOSURE:**

Kindly replace pages 5, 6 and 7 presently on file by the corresponding pages 5, 6 and 7 enclosed.

**IN THE CLAIMS:**

Kindly substitute the enclosed page containing claims 6 to 12 for the corresponding page presently on file.

**REMARKS:**

On page 5, paragraph [0013], line 4, the word "compacted" was replaced by the word --compressed--.

On page 6, paragraph [0017]:

- the word "friable" was deleted on line 2;
- on lines 3-4, words "are examples" were replaced by --is an example--; and
- on line 8, the word "harness" was corrected to read --hardness--.

On page 7, second line, the word "vibrating" was deleted.

On claim 8, reference is now to claims 1 to 7.

No new matter has been entered as a result of this amendment.

Favourable consideration of this case is respectfully requested.

Respectfully submitted,

DUCHESNAY INC.

By: Goudreau Gage Dubuc  
GOUDREAU GAGE DUBUC

Alain M. Leclerc, Patent Agent  
Goudreau Gage Dubuc  
Telephone (514) 397-7675  
Internet: [aleclerc@ggd.com](mailto:aleclerc@ggd.com)

**BRIEF DESCRIPTION OF THE DRAWING**

[0009] In the appended drawing:

[0010] Figure 1 is a flowchart of a preferred embodiment of the manufacturing method steps of the present invention.

**DESCRIPTION OF THE PREFERRED EMBODIMENT**

[0011] When used herein, the term "active ingredient" refers to a therapeutically active substance. "Therapeutically active substance" is to be understood to encompass vitamins or nutritional supplements.

[0012] When used herein, the term "medicament" refers to a pharmaceutical dosage form comprising one or more active ingredients and one or more excipients and optionally one or more coatings.

[0013] The prior art method of manufacturing Diclectin®, a medicament containing a synergistic duo of active ingredients consisted of dry mixing the active ingredients along with excipients; the mixed powder was then compressed into a tablet shape and appropriately coated.

[0014] It has now been found against expectations that the use of a roller compactor alleviates active ingredient losses during manufacturing. As an added benefit, content uniformity in terms of active ingredients is vastly improved because the particle size of active ingredients may now be standardized thereby avoiding poor mixing of active ingredients or losses due to fines which adhere to processing equipment or which do not flow properly. Indeed, roller compaction allows fine powders to be augmented to larger size particles that are less prone to cause ingredient losses during processing.

[0015] In the preferred embodiment wherein at least two active ingredients are roller compacted together, additional benefits are apparent. In such case, the powdered active ingredients are augmented in particle size in a physically combined entity of the active ingredients. This entity now resists particle segregation upon mixing and allows for improved mixing of the two active ingredients.

[0016] Referring to Figure 1, there is shown a schematic flowchart of a preferred embodiment of the process of the present invention. In general terms, in a first step 10, the active ingredients are mixed, preferably dry mixed, with at least one chosen excipient to obtain a powdered mixture. The next step 20 is to submit the powdered mixture to roller compaction to obtain a compacted product. In step 30 the compacted product is broken and sieve to a chosen mesh size. Step 40 is an optional step wherein the resulting granulate of step 30 is mixed with one or more excipients and or other active ingredients. In step 50, the resulting product from step 40 is loaded into a final dosage form such as a tablet shape obtained by compression.

[0017] A roller compactor is essentially a piece of equipment capable of compacting a powdered substance into a compacted product. The Chilsonator® sold by Fitzpatrick Company of Elmhurst, Illinois, USA is an example of such equipment. Roller compactors are commonly provided with a hopper into which the powdered substance is loaded. Counter-rotating rollers force the powdered substance between compaction rollers below or to the side of the hopper discharge. The shape of the resulting compacted product, its hardness and density are essentially dictated by the relative distance and speed of the rollers, the speed of the hopper infeed and the compaction properties of the materials being compacted.

[0018] When using a roller compactor to compact an initial blend of powdered ingredients, the resulting compacted product may be broken and

sieved to a chosen mesh size to achieve a specified granule size distribution. To this end, a breaking rotor or wheel and a mesh screen are commonly used. Fines are usually discarded or recycled back into the hopper. The resulting granulate may be further blended to ensure content uniformity of initial ingredients throughout the resulting granulate.

[0019] In essence, the compaction process removes entrapped air from interstices of the initial substance and forms denser granules when broken. Also, fine powders having poor flow characteristics and subject to electrostatic charge causing unwanted adhere to processing or storage equipment, once subjected to roller compaction, are upgraded in size to larger granules which are less prone to cause ingredient losses during processing or storage.

[0020] Furthermore, since the resulting granulate is of essentially uniform size distribution, the problem of size difference of the initial powdered ingredients is addressed. For example, the ingredient Pyridoxine HCl and Doxylamine Succinate are no longer of different mean particle diameter and are of a mean particle diameter large enough to prevent excessive loss of Pyridoxine HCl during processing.

[0021] Example 1 below is a demonstration of active ingredient loss using a prior art manufacturing method. Example 2 that follows example 1 is a demonstration that such active ingredient loss is negated when practicing the method of the present invention.

[0022] **Example 1 (prior art)**

[0023] Active ingredients, namely Pyridoxine HCl and Doxylamine Succinate were blended with exact quantities of excipients. Five samples of 3 grams were placed into small polyethylene bags and shaken. This mimics the prior art method of placing a final blend of active ingredients and excipients into

6. The method of any one of claims 1 to 5 wherein the step of forming said granular mixture into unitary dosage forms comprises compressing said granular mixture into a tablet shape.
7. The method of any one of claims 1 to 6 wherein the tablet shape is provided with a coating.
8. The method of any one of claims 1 to 7 wherein said coating is an enteric coating.
9. The method of any one of claims 1 to 5 wherein the step of forming said granular mixture into unitary dosage forms comprises loading said granular mixture into an open capsule and thereafter closing said capsule.
10. The method of any one of claims 1 to 9 wherein the active ingredients comprise Pyridoxine HCl and Doxylamine Succinate.
11. The method of any one of claims 1 to 9 wherein the active ingredients comprise equal parts of Pyridoxine HCl and Doxylamine Succinate.
12. The method of any one of claims 1 to 9 wherein the active ingredients consist of equal parts of Pyridoxine HCl and Doxylamine Succinate.



Direct Dial: (514) 397-7613  
Internet: email@ggd.com  
Your Ref.:  
Our Ref.: 11621.86

The Commissioner of Patents  
OTTAWA-HULL CANADA

Subject: Can. Pat. Appln. S.N. 2,406,592  
Filed: October 4, 2002  
Title: METHOD OF PREPARING PHARMACEUTICAL DOSAGE FORMS CONTAINING MULTIPLE ACTIVE INGREDIENTS

1 Industrie Canada Industry 1  
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Receiv Date	Serial Number
Name & Charged to	

General Partnership  
Patent and Trademark Agents

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Quebec, Canada G1R 5M8  
Telephone (418) 640-2000

Sir:

We enclose an assignment for recording against the above-noted application. Please debit the amount of \$100.00 from our Deposit Account no. 600000102.

Respectfully submitted,

Goudreau Gage Dubuc

*Ide D*

DEPOT POUR REC. GEN.  
DU CANADA 033-1325  
0681-10 09-07917  
C/A # 6102  
X124  
0733 BM 005 0001-005 10133AM 12/ 9/02 100.00

AML/fi

*W.W.*

## ASSIGNMENT OF INVENTION

### UNIVERSAL

WHEREAS, we, undersigned, **GISÈLE VEILLEUX**, residing and domiciled at 5420, rue Pasquier, Laval, Québec, Canada, H7K 2X3, **VICTOR SHULMAN**, residing and domiciled at 33, Rosemount Avenue, Thornhill, Ontario, Canada, L3T 6S8 and **ÉRIC GERVAIS**, residing and domiciled at 2526, des Oiseaux, Laval, Québec, Canada H7L 4W9, have invented certain improvements described in a patent application filed in Canada on October 4, 2002 under application number 2,406,592 and entitled:

#### METHOD OF PREPARING PHARMACEUTICAL DOSAGE FORMS CONTAINING MULTIPLE ACTIVE INGREDIENTS

and:

WHEREAS, **DUCHESNAY INC.**, a body corporate duly incorporated under the laws of the province of Québec, having its head office and principal place of business at 2925, boulevard Industriel, Laval, Québec, Canada, H7L 3W9 (hereinafter referred to as the "Assignee"), is desirous of acquiring the entire right, title and interest in and to said invention or inventions and in and to any and all patents obtained therefore in any country;

NOW, THEREFORE, in consideration of One Dollar (\$1.00) and other valuable consideration, the receipt of which is hereby acknowledged, we have and by these presents do hereby sell, assign and transfer unto said Assignee, its successors and assigns, the entire right, title and interest in and to said invention or inventions, as described in the aforesaid patents, in any form or embodiment thereof, also the entire right, title and interest in and to any and all reissues or extensions thereof to be obtained in any country upon said invention or inventions.

We further agree without any payment by said Assignee other than expenses incurred by the undersigned, to communicate to said Assignee, its representatives or agents, any facts relating to said invention or inventions, including evidence for interference purposes or for other proceedings, whenever requested; testify in any interference, litigation or other proceedings, whenever requested; and execute and deliver, on request, all lawful papers required to make any of the foregoing provisions effective, and likewise make these provisions binding upon our heirs, legal representatives, administrators and assigns.

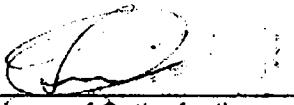
ASSIGNMENT OF INVENTION

UNIVERSAL

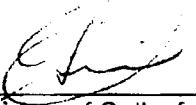
METHOD OF PREPARING PHARMACEUTICAL DOSAGE FORMS CONTAINING MULTIPLE ACTIVE INGREDIENTS

Les soussignés désirent que la présente cession soit en anglais. The undersigned request that the present assignment be in English.

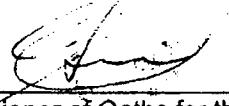
IN WITNESS WHEREOF, we have hereunto set our hands and seal this 28<sup>th</sup> day of November 2002, with a retroactive effect to October 4, 2002.

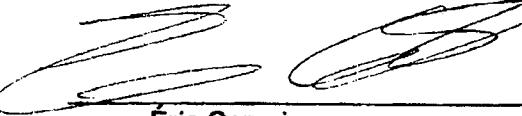
  
Commissioner of Oaths for the  
judicial district of Montreal,  
province of Quebec, Canada

  
Gisèle Veilleux

  
Commissioner of Oaths for the  
judicial district of Montreal,  
province of Quebec, Canada

  
Victor Shulman

  
Commissioner of Oaths for the  
judicial district of Montreal,  
province of Quebec, Canada

  
Eric Gervais

November 26, 2002

**GOUDREAU GAGE DUBUC**  
Tour de la Bourse  
Bureau 3400  
C.P. 242, 800 Place-Victoria  
MONTREAL Quebec  
H4Z 1E9

Application No. : **2,406,592**  
Owner : DUCHESNAY INC.  
Title : **METHOD OF PREPARING PHARMACEUTICAL DOSAGE  
FORMS CONTAINING MULTIPLE ACTIVE INGREDIENTS**  
Your File No. : **11621.86**

**EVIDENCE/COURTESY LETTER**

**Filing Date:** October 4, 2002  
**Due Date:** October 4, 2003

The applicant is advised that in the case where applicants are not the inventors, evidence, by way of affidavit, statutory declaration or copies of documents effecting transfers or changes of name establishing that the applicant is a legal representative of the inventor must be provided. Any document supplied for this purpose must be registered in the Canadian Patent Office. The fee for registration is \$100.00 per document.

The providing of evidence is not a completion requirement and no completion fee is required. However, if the documents are not received in the Canadian Patent Office on or before the due date specified above, the Patent Office will send a further letter requisitioning the required documents within a 3 month time limit set under section 25 of the Patent Rules.

Ms. Lyne Éthier  
Patent Formalities Clerk  
819-953-7554



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MONTREAL Quebec  
H4Z 1E9

Date : 2002/11/19

## FILING CERTIFICATE

<b>Application No.</b>	: 2,406,592	<b>Filing Date</b>	: 2002/10/04
<b>Expected Laid-Open Date</b>	: 2004/04/04	<b>Your Reference</b>	: 11621.86
<b>Title of Invention</b>	: METHOD OF PREPARING PHARMACEUTICAL DOSAGE FORMS CONTAINING MULTIPLE ACTIVE INGREDIENTS		
<b>Applicant(s)</b>	: DUCHESNAY INC.		
<b>Inventor(s)</b>	: VEILLEUX, GISELE; SHULMAN, VICTOR; GERVAIS, ERIC		

### Special Notice

You are reminded that annual fees to maintain your application are needed for each one-year period between the 2nd and 20th anniversaries and must be paid on or before each anniversary. Failure to pay within the prescribed time limit will lead to abandonment of your application.

Commissioner of Patents

Canada

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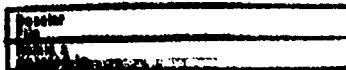
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OPIC CIPO

Direct Dial: (514) 397-7613  
Internet: email@ggd.com  
Your Ref.:  
Our Ref.: 11621.86

OCT 04 2002 2 8 1



October 4, 2002

The Commissioner of Patents  
OTTAWA-HULL CANADA

Subject: Inventor: VEILLEUX, Gisèle et al  
Applicant: DUCHESNAY INC.  
Title: METHOD OF PREPARING PHARMACEUTICAL DOSAGE  
FORMS CONTAINING MULTIPLE ACTIVE INGREDIENTS

Sir:

General Partnership  
Patent and Trademark Agents

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140 Grande Allée Est  
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Telephone (418) 640-2000

We enclose for filing a patent application consisting of the following documents and fees:

- Petition
- Abstract
- Disclosure and claims
- Drawings
- Fees: Filing \$300.00

C/A # 6102  
K121  
8914 BM 012 0001-001 10:00AM 10/ 9/02  
300.00

Priority is hereby claimed, based on:

S.N.: n/a  
Date: n/a  
Country: n/a

Please debit the amount of \$300.00 from our Deposit Account no. 600000102.

Respectfully submitted,

Goudreau Gage Dubuc

AML/f

**PETITION FOR GRANT OF A PATENT**

1 Industrie Canada OPIC 1 Industry Canada CIPO

1. The applicant DUCHESNAY INC.

OCT 04 2002 2 8 1

whose complete address is 2925, boulevard Industriel, Chomedey, Laval, Quebec, Canada H7L 3W9

requests the grant of a patent for an invention, entitled "**METHOD OF PREPARING PHARMACEUTICAL DOSAGE FORMS CONTAINING MULTIPLE ACTIVE INGREDIENTS**"

which is described and claimed in the accompanying specification.

2. This application is a division of application number filed in Canada on.

3. (1) The applicant is the sole inventor.

(2) The inventors 1) VEILLEUX, Gisèle; 2) SHULMAN, Victor; and  
3) GERVAIS, Éric

whose complete addresses are 1) 5420, rue Pasquier, Laval, Quebec, Canada H7K 2X3;  
2) 33 Rosemount Avenue, Thornhill, Ontario, Canada L3T 6S8; and 3) 2526, boulevard des  
Oiseaux, Laval, Quebec, Canada H7L 3W9

and the applicant own in Canada the whole interest in the invention.

4. The applicant requests priority in respect of the application on the basis of the following previously regularly filed application:

Country of filing	Application number	Filing date
n/a	n/a	n/a

5. The applicant appoints **GOUDREAU GAGE DUBUC** whose complete address in Canada is 3400, The Stock Exchange Tower, P.O. Box 242, Victoria Square, Montreal, Quebec H4Z 1E9, telephone (514) 397-7602, telecopier (514) 397-4382, Canada, as the applicant's representative in Canada, pursuant to section 29 of the Patent Act.

6. The applicant appoints **GOUDREAU GAGE DUBUC**, whose complete address is 3400, The Stock Exchange Tower, P.O. Box 242, Victoria Square, Montreal, Quebec H4Z 1E9, telephone (514) 397-7602, telecopier (514) 397-4382, Canada, as the applicant's patent agent.

7. The applicant believes that the applicant is entitled to claim status as a "small entity" as defined under section 2 of the Patent Rules.

8. The applicant requests that Figure No. 1 of the drawings accompany the abstract when it is open to public inspection under section 10 of the Patent Act or published.

Signed at MONTREAL QUEBEC CANADA

this 4<sup>th</sup> day of October 2002

DUCHESNAY INC.

Bv:

**ABSTRACT OF THE DISCLOSURE**

A method for the preparation of pharmaceutical dosage forms comprising multiple powdered active ingredients, in a preferred embodiment, said method comprising the steps of mixing said active ingredients and at least one chosen excipient so as to obtain a powdered mixture; compacting said powdered mixture in a roller-compactor apparatus to obtain a compacted product; breaking and sieving said compacted product to a chosen mesh size to obtain similar sized granules; preferably dry mixing said granules with at least one chosen excipient so as to obtain a granular mixture; forming said granular mixture into unitary dosage forms.

**TITLE OF THE INVENTION**

Method of preparing pharmaceutical dosage forms containing multiple active ingredients

**FIELD OF THE INVENTION**

**[0001]** The present invention relates to a method of preparing pharmaceutical dosage forms containing multiple active ingredients. More specifically, the present invention is concerned with alleviating active ingredient losses during manufacturing and ensuring content uniformity of dosage forms.

**BACKGROUND OF THE INVENTION**

**[0002]** A number of pharmaceutical dosage forms comprise multiple active ingredients. One example is the anti-nauseant medicament prescribed during pregnancy currently sold in Canada under the trademark Diclectin®.

**[0003]** Diclectin® is a medicament containing a synergistic duo of active ingredients, namely Doxylamine Succinate and Pyridoxine HCl. In the case of Diclectin®, the approved label of the product calls for the duo of active ingredients to be present in exactly equal amounts of 10 mg. These active ingredients are obtained in the form of powders having different granular sizes which makes it very difficult to uniformly mix them in a dry state along with required excipients. Such phenomenon is generally caused by particle segregation during mixing. This poses a content uniformity challenge during manufacturing of final dosage forms.

**[0004]** An added challenge to content uniformity is the loss of the active ingredient Pyridoxine HCl during manufacturing of Diclectin®. Pyridoxine HCl is generally provided as a crystalline powder having a mean particle diameter of about 60 microns. In contrast, Doxylamine Succinate is

composed of rod shaped particles having a mean particle diameter of about 200 microns. It has been observed that due to their small size and possible electrostatic charge, Pyridoxine HCl particles tend to easily adhere to manufacturing vessels and other processing or storage equipment. Thus, when processing both active ingredients through the same equipment, more Pyridoxine HCl is lost than Doxylamine Succinate. To compensate for this effect, operators have commonly used a 8-10 weight percent overage of Pyridoxine HCl in comparison to Doxylamine Succinate. However, the result of such method is somewhat irregular and quality controls still reject many lots.

**[0005]** In general terms, whenever preparing multi-ingredient medicaments, it is important that manufacturing methods allow for the final content of each dosage form to follow rather exactly the contents announced on the label. This is indeed a legal and regulatory requirement in most countries of the world.

**[0006]** Thus, there is a need for a method of manufacturing Diclectin® or other similar powderous multi-ingredient medicaments which alleviate ingredient losses during manufacturing and provides superior content uniformity results when compared to known methods.

#### **OBJECTS OF THE INVENTION**

**[0007]** Objects of the present invention are therefore to provide an improved method of preparing pharmaceutical dosage forms containing multiple active ingredients so as to ensure active ingredient content uniformity and to alleviate active ingredient losses during manufacturing.

**SUMMARY OF THE INVENTION**

More specifically, in accordance with the present invention, there is provided a method for the preparation of pharmaceutical dosage forms comprising multiple powdered active ingredients, said method comprising the steps of:

- (a) mixing said active ingredients and at least one chosen excipient so as to obtain a powdered mixture;
- (b) compacting said powdered mixture in a roller compactor apparatus to obtain a compacted product;
- (c) breaking and sieving said compacted product to a chosen mesh size to obtain similar sized granules;
- (d) forming said granules into unitary dosage forms.

In another aspect, the method may comprise the steps of:

- (a) mixing said active ingredients and at least one chosen excipient so as to obtain a powdered mixture;
- (b) compacting said powdered mixture in a roller compactor apparatus to obtain a compacted product;
- (c) breaking and sieving said compacted product to a chosen mesh size to obtain similar sized granules;
- (d) mixing said granules with at least one chosen excipient so as to obtain a granular mixture;
- (e) forming said granular mixture into unitary dosage forms.

In yet another aspect, the method may comprise the steps of:

- (a) mixing said active ingredients so as to obtain a powdered mixture;
- (b) compacting said powdered mixture in a roller compactor apparatus to obtain a compacted product;
- (c) breaking and sieving said compacted product to a chosen mesh size to obtain similar sized granules;
- (d) mixing said granules with at least one chosen excipient so as to obtain a granular mixture;
- (e) forming said granular mixture into unitary dosage forms.

In yet another aspect, the method may comprise the steps of:

- (a) mixing at least one of said active ingredients and at least one excipient so as to obtain a powdered mixture;
- (b) compacting said powdered mixture in a roller compactor apparatus to obtain a compacted product;
- (c) breaking and sieving said compacted product to a chosen mesh size to obtain similar sized granules;
- (d) mixing said granules with at least one other active ingredient so as to obtain a granular mixture;
- (e) forming said granular mixture into unitary dosage forms.

In yet another aspect, the method may comprise the steps of:

- (a) mixing at least one of said active ingredients and at least one excipient so as to obtain a powdered mixture;
- (b) compacting said powdered mixture in a roller compactor apparatus to obtain a compacted product;
- (c) breaking and sieving said compacted product to a chosen mesh size to obtain similar sized granules;
- (d) mixing said granules with at least one other active ingredient and at least one other excipient so as to obtain a granular mixture;
- (e) forming said granular mixture into unitary dosage forms.

[0008] Other aspects, objects, advantages and features of the present invention will become more apparent upon reading of the following non-restrictive description of preferred embodiments thereof, given by way of example only with reference to the accompanying drawing.

**BRIEF DESCRIPTION OF THE DRAWING**

[0009] In the appended drawing:

[0010] Figure 1 is a flowchart of a preferred embodiment of the manufacturing method steps of the present invention.

**DESCRIPTION OF THE PREFERRED EMBODIMENT**

[0011] When used herein, the term "active ingredient" refers to a therapeutically active substance. "Therapeutically active substance" is to be understood to encompass vitamins or nutritional supplements.

[0012] When used herein, the term "medicament" refers to a pharmaceutical dosage form comprising one or more active ingredients and one or more excipients and optionally one or more coatings.

[0013] The prior art method of manufacturing Diclectin®, a medicament containing a synergistic duo of active ingredients consisted of dry mixing the active ingredients along with excipients; the mixed powder was then compacted into a tablet shape and appropriately coated.

[0014] It has now been found against expectations that the use of a roller compactor alleviates active ingredient losses during manufacturing. As an added benefit, content uniformity in terms of active ingredients is vastly improved because the particle size of active ingredients may now be standardized thereby avoiding poor mixing of active ingredients or losses due to fines which adhere to processing equipment or which do not flow properly. Indeed, roller compaction allows fine powders to be augmented to larger size particles that are less prone to cause ingredient losses during processing.

[0015] In the preferred embodiment wherein at least two active ingredients are roller compacted together, additional benefits are apparent. In such case, the powdered active ingredients are augmented in particle size in a physically combined entity of the active ingredients. This entity now resists particle segregation upon mixing and allows for improved mixing of the two active ingredients.

[0016] Referring to Figure 1, there is shown a schematic flowchart of a preferred embodiment of the process of the present invention. In general terms, in a first step 10, the active ingredients are mixed, preferably dry mixed, with at least one chosen excipient to obtain a powdered mixture. The next step 20 is to submit the powdered mixture to roller compaction to obtain a compacted product. In step 30 the compacted product is broken and sieve to a chosen mesh size. Step 40 is an optional step wherein the resulting granulate of step 30 is mixed with one or more excipients and/or other active ingredients. In step 50, the resulting product from step 40 is loaded into a final dosage form such as a tablet shape obtained by compression.

[0017] A roller compactor is essentially a piece of equipment capable of compacting a powdered substance into a friable compacted product. The Chilsonator® sold by Fitzpatrick Company of Elmhurst, Illinois, USA are examples of such equipment. Roller compactors are commonly provided with a hopper into which the powdered substance is loaded. Counter-rotating rollers force the powdered substance between compaction rollers below or to the side of the hopper discharge. The shape of the resulting compacted product, its harness and density are essentially dictated by the relative distance and speed of the rollers, the speed of the hopper infeed and the compaction properties of the materials being compacted.

[0018] When using a roller compactor to compact an initial blend of powdered ingredients, the resulting compacted product may be broken and

sieved to a chosen mesh size to achieve a specified granule size distribution. To this end, a breaking rotor or wheel and a vibrating mesh screen are commonly used. Fines are usually discarded or recycled back into the hopper. The resulting granulate may be further blended to ensure content uniformity of initial ingredients throughout the resulting granulate.

**[0019]** In essence, the compaction process removes entrapped air from interstices of the initial substance and forms denser granules when broken. Also, fine powders having poor flow characteristics and subject to electrostatic charge causing unwanted adhere to processing or storage equipment, once subjected to roller compaction, are upgraded in size to larger granules which are less prone to cause ingredient losses during processing or storage.

**[0020]** Furthermore, since the resulting granulate is of essentially uniform size distribution, the problem of size difference of the initial powdered ingredients is addressed. For example, the ingredient Pyridoxine HCl and Doxylamine Succinate are no longer of different mean particle diameter and are of a mean particle diameter large enough to prevent excessive loss of Pyridoxine HCl during processing.

**[0021]** Example 1 below is a demonstration of active ingredient loss using a prior art manufacturing method. Example 2 that follows example 1 is a demonstration that such active ingredient loss is negated when practicing the method of the present invention.

**[0022]** **Example 1 (prior art)**

**[0023]** Active ingredients, namely Pyridoxine HCl and Doxylamine Succinate were blended with exact quantities of excipients. Five samples of 3 grams were placed into small polyethylene bags and shaken. This mimics the prior art method of placing a final blend of active ingredients and excipients into

Polyethylene lined drums prior to emptying said drums into the hopper of a tablet compression machine. After being placed in the small polyethylene bags, the samples were removed and analyzed for content of active ingredients. The results are shown in Table I below:

**Table I – Content analysis compared to initial quantity being 100%wt of each of Pyridoxine HCl and Doxylamine Succinate.**

Note: values above 100% are attributable to the detection limit of the analysis apparatus.

SAMPLE No.	PYRIDOXINE HCL IN WT%	DOXYLAMINE SUCCINATE IN WT%
1	76.6	101.3
2	77.6	104.1
3	85.9	101.4
4	85.3	101.4
5	87.1	101.6
Average loss	17.5%	Nil

**[0024]** This example clearly shows how Pyridoxine HCl is prone to loss during processing and storage. Example 2 below shows how this problem is avoided by the method of the present invention.

**[0025] Example 2**

**[0026]** The active ingredients, namely Pyridoxine HCl and Doxylamine Succinate were blended with exact quantities of excipients as in Example 1. However, this time the blend was processed using a Chilsonator® Roller compactor to form compacted products that were then crushed and screened to 16 mesh. A series of six 3 grams samples were collected. Two of the samples were directly analyzed for active ingredient content. The four remaining samples were placed in small polyethylene bags and shaken as in Example 1. The samples were then removed from the bags and analyzed for active ingredient content.

**[0027]** The results are shown in Table II below:

**Table II – Content analysis compared to control quantity being about 68.8mg of Pyridoxine HCl per gram of mixture and about 67.5mg of Doxylamine Succinate per gram of mixture.**

Note: values above 100% are attributable to the detection limit of the analysis apparatus.

SAMPLE No.	PYRIDOXINE HCL	DOXYLAMINE SUCCINATE
1 (control)	68.6 mg/g	67.9 mg/g
2 (control)	68.9mg/g	67.1 mg/g
Average of 1 (control) and 2 (control)	68.8mg/g or 100wt%	67.5mg/g or 100wt%
3	95.1 wt% vs. control	99.6 wt% vs. control

SAMPLE No.	PYRIDOXINE HCl	DOXYLAMINE SUCCINATE
4	95.5 wt% vs. control	100.6 wt% vs. control
5	97.1 wt% vs. control	100.4 wt% vs. control
6	96.5 wt% vs. control	99.4 wt% vs. control
Average loss	3.9 wt% vs. control	Nil

**[0028]** These results demonstrate that by using the manufacturing method of the present invention, the average loss of Pyridoxine HCl was dramatically lowered when compared to the prior art method.

**[0029]** It is also to be understood that the method of the present invention can also involve the step of blending the granules resulting from roller compaction to further increase content uniformity of the granular blend. This is done prior to compression into tablet shape or prior to placing the granules in some other suitable dosage form.

**[0030]** It is also to be understood that the method of the present invention can involve mixing the active ingredients alone, i.e. without excipients, and submitting the active ingredients to roller compaction prior to blending the compacted granules with at least one excipient.

**[0031]** It is also to be understood that the method of the present invention can involve mixing a single active ingredient (usually the smaller sized active ingredient) with at least one excipient and submitting the mixture to roller compaction prior to blending the compacted granules with at least one other active ingredient and perhaps other excipients.

[0032] It is also to be understood that all mixing steps can be accomplished as sequential mixing of various ingredients with or without intervening sieving or pre-blending steps. The term "mixing" is used in its broad sense of creating a mixture regardless of the exact processing steps used to obtain this mixture.

[0033] When compressed into tablet shape as for an oral or sublingual dosage form, the tablet can be sealed or otherwise coated such as with an enteric coating. The exact coating will of course depend on the intended release site and release rate of the active ingredients once the tablet is ingested.

[0034] Although the present invention has been described hereinabove by way of preferred embodiments thereof, it can be modified, without departing from the spirit and nature of the subject invention as defined in the appended claims.

**WHAT IS CLAIMED IS:**

1. A method for the preparation of pharmaceutical dosage forms comprising multiple powdered active ingredients, said method comprising the steps of:
  - 5 (a) mixing said active ingredients and at least one chosen excipient so as to obtain a powdered mixture;
  - (b) compacting said powdered mixture in a roller compactor apparatus to obtain a compacted product;
  - (c) breaking and sieving said compacted product to a chosen mesh size to obtain similar sized granules;
  - 10 (d) forming said granules into unitary dosage forms.
2. A method for the preparation of pharmaceutical dosage forms comprising multiple powdered active ingredients, said method comprising the steps of:
  - 15 (a) mixing said active ingredients and at least one chosen excipient so as to obtain a powdered mixture;
  - (b) compacting said powdered mixture in a roller compactor apparatus to obtain a compacted product;
  - (c) breaking and sieving said compacted product to a chosen mesh size to obtain similar sized granules;
  - 20 (d) mixing said granules with at least one chosen excipient so as to obtain a granular mixture;
  - (e) forming said granular mixture into unitary dosage forms.
- 25 3. A method for the preparation of pharmaceutical dosage forms comprising multiple powdered active ingredients, said method comprising the steps of:
  - (a) mixing said active ingredients so as to obtain a powdered mixture;
  - 30 (b) compacting said powdered mixture in a roller compactor apparatus to obtain a compacted product;

- (c) breaking and sieving said compacted product to a chosen mesh size to obtain similar sized granules;
- (d) mixing said granules with at least one chosen excipient so as to obtain a granular mixture;
- 5 (e) forming said granular mixture into unitary dosage forms.

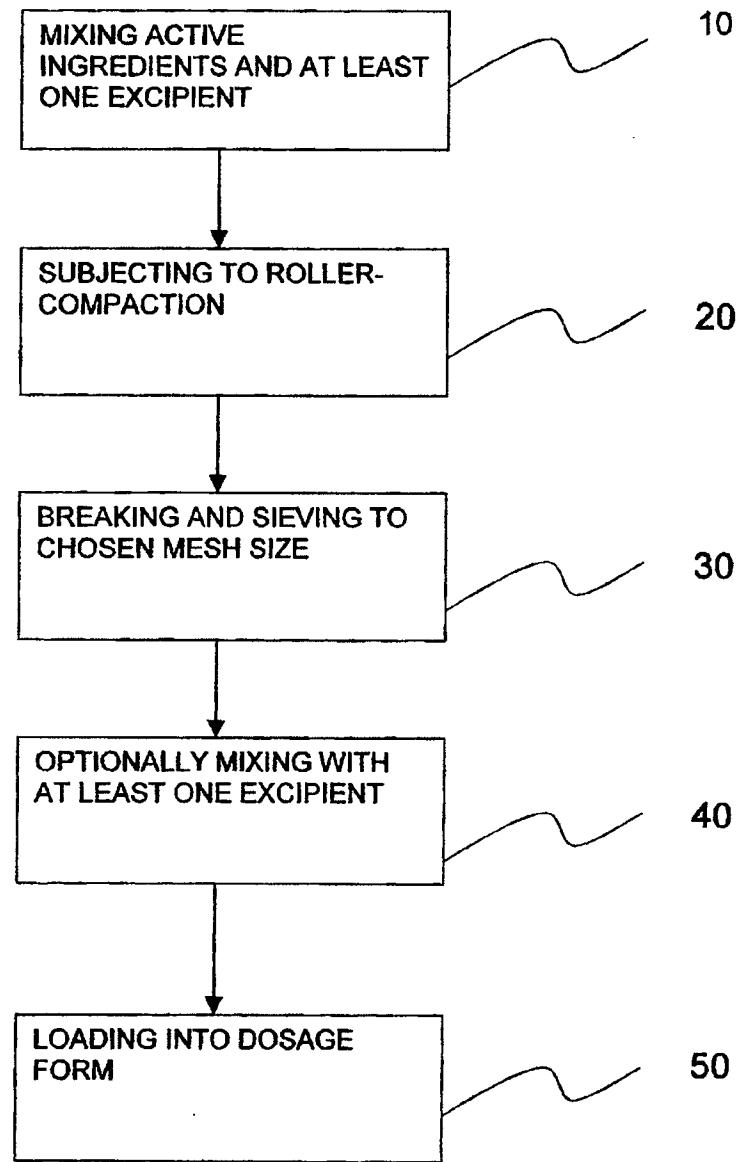
4. A method for the preparation of pharmaceutical dosage forms comprising multiple powdered active ingredients, said method comprising the steps of:

- 10 (a) mixing at least one of said active ingredients and at least one excipient so as to obtain a powdered mixture;
- (b) compacting said powdered mixture in a roller compactor apparatus to obtain a compacted product;
- (c) breaking and sieving said compacted product to a chosen mesh size to obtain similar sized granules;
- 15 (d) mixing said granules with at least one other active ingredient so as to obtain a granular mixture;
- (e) forming said granular mixture into unitary dosage forms.

20 5. A method for the preparation of pharmaceutical dosage forms comprising multiple powdered active ingredients, said method comprising the steps of:

- (a) mixing at least one of said active ingredients and at least one excipient so as to obtain a powdered mixture;
- 25 (b) compacting said powdered mixture in a roller compactor apparatus to obtain a compacted product;
- (c) breaking and sieving said compacted product to a chosen mesh size to obtain similar sized granules;
- (d) mixing said granules with at least one other active ingredient and at least one other excipient so as to obtain a granular mixture;
- 30 (e) forming said granular mixture into unitary dosage forms.

6. The method of any one of claims 1 to 5 wherein the step of forming said granular mixture into unitary dosage forms comprises compressing said granular mixture into a tablet shape.
7. The method of any one of claims 1 to 6 wherein the tablet shape is provided with a coating.  
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8. The method of any one of claims 1 to 6 wherein said coating is an enteric coating.
9. The method of any one of claims 1 to 5 wherein the step of forming said granular mixture into unitary dosage forms comprises loading said granular mixture into an open capsule and thereafter closing said capsule.  
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10. The method of any one of claims 1 to 9 wherein the active ingredients comprise Pyridoxine HCl and Doxylamine Succinate.
- 15 11. The method of any one of claims 1 to 9 wherein the active ingredients comprise equal parts of Pyridoxine HCl and Doxylamine Succinate.
12. The method of any one of claims 1 to 9 wherein the active ingredients consist of equal parts of Pyridoxine HCl and Doxylamine Succinate.



*FIGURE 1*